UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 3 DECEMBER 2001

SUBJECT: **DIFLUFENZOPYR plus DICAMBA** - Exposure/Risk Assessment from the Proposed New Uses of Distinct® Herbicide on Pop Corn, Sweet Corn, and Pasture or Rangeland. DP Code: D276174 PC Codes: 5107, 29801.

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INTRODUCTION

The BASF Corporation, Agricultural Products, has submitted requests for registration of Distinct® herbicide for controlling annual and perennial broad leaf weed species in pop corn, sweet corn, and pasture or rangeland. This memorandum presents the Health Effects Division's estimate of pesticide handler exposures and risks that might result from the proposed new uses.

Distinct® is a wettable granule herbicide that is comprised of 0.20 lb acid equivalent diflufenzopyr per pound of product and 0.50 lb acid equivalent dicamba per pound of product. The proposed new uses comprise an amendment to the EPA Registered Product No. 7969-150 which is registered for use on field corn and non-crop areas.

For Pop corn and Sweet corn, applications may be made from pre-plant to post-emergence when corn is up to 24" tall. For Pasture or Rangeland, applications should be made when weeds are actively growing. For biannual or perennial weeds, make applications when weeds are in the rosette stage before bolting, in the bud stage or in the fall prior to a killing frost. Table 1.0

contains a summary of the proposed new use patterns.

Table 1.0 Use Pattern Summary of Proposed New Uses of Distinct® Herbicide on Pop Corn, Sweet Corn, and Pasture or Rangeland	
Formulation	Wettable Granule; diflufenzopyr 0.20 lb acid equivalent/ lb product; dicamba 0.50 lb acid equivalent/ lb product.
Use Site	Pop Corn, Sweet Corn, Pasture, Rangeland
Application Method	ground
Maximum Application Rate* **pounds acid equivalent/A** SEE "Note:" BELOW	Sweet corn - 0.25 lb **product**/A Pop corn and Pasture/Range - 0.5 lb **product**/A **seasonal max -** Sweet corn 0.375 lb **product**/A Pop corn 0.63 lb **product**/A Pasture/Range 0.5 lb **product**/A
Frequency/Timing	two application/season; 14 day interval
PHI	Sweet corn = 72 days dry grain and stover; 32 days for ears and stover. Pop corn = 72 days for grain or stover; 32 days for forage. Pasture/Range = NO PHI
REI	label lists 12 hours (?) needs clarification see page 5 "Restricted Entry Interval"
Manufacturer	BASF Corporation

*
Sweet corn max rate = 4 oz product/A = 0.25 lb product/A * 0.2 lb a.e./lb product diflufenzopyr = 0.05 lb a.e./A and * 0.50 lb a.e./lb product dicamba = 0.125 lb a.e./A
Pop corn and Pasture/Range max rate = 8 oz product/A = 0.5 lb product/A * 0.2 lb a.e./lb product diflufenzopyr = 0.10 lb a.e./A and * 0.50 lb a.e./pound product dicamba = 0.25 lb a.e./A

Note: There is a discrepancy between the submitted Petition Section B and the Supplemental Label concerning the proposed maximum single and seasonal application rates on pop corn and grass. The Section B reads "Pasture and popcorn have a maximum single application rate of 8 ounces per acre with a maximum seasonal use of 10 ounces per acre." The Supplemental Label reads 1) for pasture and rangeland "Do not exceed 8 ounces of Distinct-® per acre per calendar year" and 2) for pop corn "Apply 4 to 6 ounces of Distinct-® per acre....." and no maximum

seasonal application rate is specified. Per personal communication with BASF, the appropriate maximum single and seasonal application rates for pop corn are 8 oz. Distinct-®/A (0.1 lb. diflufenzopyr/A) and 10 oz. Distinct-®/A (0.125 lb. diflufenzopyr/A), respectively; and the appropriate maximum seasonal application rate on grass is 8 oz. Distinct-®/A (0.1 lb. diflufenzopyr/A) (personal communication between J. Tyler and M. Graben; 11/2/01). These proposed application rates are reflected in this document.

HANDLER EXPOSURE

According to the Reference Files System (REFS v. 2.3, 12 July 01), dicamba (3,6-Dichloro-o-anisic acid) is registered for use on field corn, pop corn, sorghum, pastures and rangeland, small grains, golf courses, ornamental lawns and turf including residential, numerous species of grass, ornamentals, various rights of way, and institutional and industrial sites. Diflufenzopyr is registered for use on field corn. This assessment addresses the registration of dicamba on sweet corn and diflufenzopyr on sweet corn, pop corn, and pasture/rangeland. **NOTE** that neither the registered product (EPA Reg. No. 7969-150) **nor** the proposed label amendment language (Supplemental label wjm 5-9-00 NVA 2000-04-078-0056) include directions for use in aerial application and precludes use in any irrigation system. The estimates of pesticide handler exposure are therefore limited here to a mixer/loader using open pour, dry flowable material and an applicator using open cab, ground boom equipment. No chemical specific data were available with which to assess pesticide handler exposure therefore data were used from studies contained in the Pesticide Handlers Exposure Database (PHED) Surrogate Table (v1.1., 1998). It is HED policy to present pesticide handler dermal exposure where handlers wear a single layer of clothing (i.e., long sleeve shirt, long pants and shoes plus socks) and with or without gloves.

In a report dated 15 January 1998, the Health Effects Division Hazard Identification Assessment Review Committee (HIARC) identified toxicological endpoints for use in risk assessment **of dicamba**. Dicamba technical is in toxicity category III for acute oral and dermal toxicity, category IV for acute inhalation, category II for ocular and dermal irritation. It is not a dermal sensitizer. Short- and intermediate-term dermal No Adverse Effect Levels (NOAELs) of 1,000 mg a.i./kg bw/day were identified from 21 day dermal toxicity studies in the rabbit. No inhalation endpoints were established for any time period. Dicamba was described as a "Not Classifiable Human Carcinogen since there were no acceptable data in mice and rats at doses adequate to assess the carcinogenic potential."

In a 24 September 1998 memorandum (M. Ottley et al., DP 249097) HED assessed the exposures and risks from the uses of dicamba on asparagus, corn, cotton, grass forage and hay, wheat forage and hay, preharvest use on wheat, barley and soybeans. In that assessment an FQPA Uncertainty Factor of 3 (three) was applied to the Margins Of Exposure for occupational (i.e., pesticide handler) exposures. FQPA policy has changed and FQPA UFs are not applied to occupational exposures. Therefore, the minimum level of concern for occupational exposure in this case, is for MOEs of <100.

On 18 October 2001, the HIARC met to review acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. "The purpose of this meeting was to select the toxicological endpoints for incidental oral residential exposure and to re-evaluate the endpoints selected for dermal and inhalation occupational/residential risk assessments under the new definition of short-term (1-30 days), intermediate-term (1-6 months) and long-term (6 months - lifetime)." The HIARC identified NOAELS for incidental oral as well as short- and intermediate-term oral exposures. A NOAEL was identified for short- intermediate- and long-term exposures for the dermal and inhalation routes. The NOAEL (45 mg/kg bw/day) is the same for the routes and durations of exposure noted above. The HIARC also identified a dermal absorption factor of 15% applicable to dermal exposures. See Appendix I for a summary of toxicological endpoints.

The 1998 memorandum by Ottley et al. includes an assessment of residential exposures and risk from application as well as for post-application. The report states: "Residential exposures may occur from dicamba uses for weed control on residential and recreational turf. Liquid and granular formulations containing dicamba as an active ingredient are registered for turf and ornamental uses (REFS, 08/1998). Based on information from REFS, liquid end use products containing approximately 4% dicamba, and granular end use products containing approximately 0.5% dicamba, are representative of home use type products." Residential "applicator" and post-application exposures resulted in MOEs that were higher than HEDs levels of concern. A golf course re-entry exposure estimate was not conducted. In view of the MOE's for residential applicator and residential post-application re-entry, HED believes a golf course re-entry assessment is not necessary since resulting MOE's are not expected to be less than those for the residential applicator in particular.

On 24 September 1998, the HED HIARC met to discuss the adequacy of the toxicology database with respect to the compound **diflufenzopyr** (Memo, W. Dykstra et al., 6 October 1998, HED Doc. No. 012894). Diflufenzopyr is in toxicity category IV for acute oral, dermal and inhalation toxicity, category III for primary eye irritation, category IV for primary skin irritation and it is not a dermal sensitizer. Diflufenzopyr is classified as "Not Likely" to be a human carcinogen. Short, Intermediate and Long-term dermal toxicological endpoints were **not** identified as "no dermal or systemic toxicity was seen at 1000 mg/kg/day in the 21 day dermal toxicity study in rabbits." Short-term and Intermediate-term inhalation toxicity endpoints were established (58 mg/kg/day based on subchronic feeding studies in dogs where compensated hemolytic anemia was observed in both sexes). A long-term inhalation toxicity endpoint was not identified. See Appendix II for summary tables of toxicity for diflufenzopyr. A Margin of Exposure (MOE) of 100 is adequate to ensure the safety of pesticide handlers in this case. See Appendix II for a summary of toxicological endpoint selection for diflufenzopyr.

Since the HIARC did not identify dermal toxicological endpoints of concern, citing no effects at the limit dose of 1000 mg/kg bw/day, assessment of risk to pesticide handlers via the dermal route is not necessary and therefore not presented here. An assessment of exposure and risk is presented for pesticide handlers via the inhalation route since the only toxicological endpoint of

concern that was identified, is for short and intermediate term inhalation exposure to diflufenzopyr.

Based on the preceding information, estimates of exposure and risk were conducted for a mixer/loader and an applicator. See Tables 2.0 and 2.1 for summaries of findings.

Table 2.0 Estimated Exposures and Risk to Pesticide Handlers Applying *DIFLUFENZOPYR* In Distinct® Herbicide to Sweet Corn, Pop Corn and Pasture/Rangeland

Unit Exposure[1] mg a.i./lb handled	Application Rate[2] lb a.i. handled/A	Units Treated[3]	Avg. Daily Dose[4] mg a.i./kg bw/day	NOAEL[5] mg a.i./kg bw/day	MOE[6]
Mixer/Loader - Dry Flowable - Open Pour					
INHALAT. 0.00077 HC	0.10	200 A/day	$2.2X10^{-4}$	58	263,600
Applicator - Ground Boom - Open Cab					
INHALAT 0.00074 HC	0.10	200 A/day	$2.1X10^{-4}$	58	276,190

1. Unit Exposure = mg a.i./lb a.i. handled; taken from the Pesticide Handler's Exposure Database PHED Surrogate Exposure Guide version 1.1; August 1998; Inhalat. = Inhalation. HC = high confidence data;
2. Application Rate from proposed amendments to EPA Reg No. 7969-150. The highest rate of application is to pop corn and pasture/range; 8 oz **product**/A = 0.5 lb **product**/A ∴ 0.5 lb product/A * 0.20 lb a.e. diflufenzopyr/lb product = 0.10 lb a.e./A
3. Acres Treated are derived from EXPO Sci.Adv.Coun Pol. No. 9.
4. Average Daily Dose (ADD) = Unit Exposure * Application Rate * Units Treated ÷ 70 kg body weight. Inhalation exposure assumes 100% inhalation absorption.
5. NOAEL = No Observed Adverse Effect Level (mg a.i./kg bw/day). For diflufenzopyr, the short- and intermediate- term inhalation endpoint is 58 mg a.i./kg bw/day.
6. Margin of Exposure (MOE) = NOAEL ÷ ADD

Table 2.1 Estimated Exposures and Risk to Pesticide Handlers Applying *DICAMBA* In Distinct® Herbicide to Sweet Corn, Pop Corn and Pasture/Rangeland					
Unit Exposure[1] mg a.i./lb handled	**Application Rate**[2] lb a.i. handled/A	**Units Treated**[3]	**Avg. Daily Dose**[4] mg a.i./kg bw/day	**NOAEL**[5] mg a.i./kg bw/day	**COMBINED MOE**[6]
Mixer/Loader - Dry Flowable - Open Pour					
DSLNG 0.066 LC DSLWG 0.066 HC INHAL 0.00077 HC	0.25	200 A/day	0.0083 0.0083 0.00064	45	5100
Applicator - Ground Boom - Open Cab					
DSLNG 0.014 HC DSLWG 0.014 HC INHAL 0.00074 HC	0.25	200 A/day	0.0018 0.0018 0.00062	45	18,800

1. Unit Exposure = mg a.i./lb a.i. handled; taken from the Pesticide Handler's Exposure Database PHED Surrogate Exposure Guide version 1.1; August 1998; DSLNG = Dermal Single Layer **NO** Gloves; DSLWG = Dermsal Single Layer **WITH** Gloves; Inhalat. = Inhalation. HC = high confidence data;
2. Application Rate from proposed amendments to EPA Reg No. 7969-150. The highest rate of application is to pop corn and pasture/range; 8 oz **product**/A = 0.5 lb **product**/A ∴ 0.5 lb product/A * 0.5 lb a.e./lb product dicamba = 0.25 lb a.i. (acid equivalent)/A
3. Acres Treated are derived from Sci.Adv.Coun Pol. No. 9.
4. Average Daily Dose (ADD) = Unit Exposure * Application Rate * Units Treated * 15 % Dermal Absorption ÷ 60 kg body weight. Inhalation exposure assumes 100% inhalation absorption.
5. NOAEL = No Adverse Effect Level (mg a.i./kg bw/day). For dicamba, short- intermediate- and long-term dermal and inhalation NOAEL = 45 mg a.i./kg bw/day.
6. Margin of Exposure (MOE) = NOAEL ÷ ADD. Since the toxicological endpoints are the same, identified from the same study and for the same effect, exposures are aggregated and the MOE is expressed as a "Combined" MOE.

All Margins of Exposure (MOEs) for pesticide handlers are ≥ 100 therefore the estimated risks do not exceed HEDs level of concern.

POST-APPLICATION WORKER EXPOSURE

Since no dermal toxicological endpoints were identified for diflufenzopyr, it is not necessary to estimate worker post-application exposure to diflufenzopyr. However, dermal toxicological endpoints are identified for **dicamba** therefore, a description of post-application exposure and risk to dicamba are presented below. Distinct® herbicide is applied at the pre-emergence or early post-emergence stages of weed growth, therefore the most likely post-application exposure

activities that might occur in sweet corn or pop corn are scouting or irrigation activities (Science Advisory Council for Exposure [EXPOSAC] Policy No. 003.1 Revised 7 August 2000). The Transfer Coefficients (TC) identified in conjunction with the Agricultural Re-Entry Task Force for those activities are 1000 cm^2/hr each. Those are the highest TCs identified for any activity that might occur at that stage of crop development. In the case of pasture and rangeland, HED believes it is unlikely that irrigation activities would occur as might for row crops. The EXPOSAC and the ARTF have not identified TCs applicable to post-application activities associated with pasture and rangeland. However, in HEDs opinion, scouting may occur. HED believes that scouting pasture and rangeland would not result in TCs higher than what are identified from study data for corn as described above.

There are no compound specific data with which to estimate post-application agricultural worker exposures incurred while performing scouting or irrigation activities. In cases such as this, HED uses standard default assumptions to estimate a "Tier I" screening level exposure assessment. The TC's are identified from study data in the same or similar cropping systems. HED further assumes (based on study data in agricultural systems) that 20% of the application rate is available as foliar dislodgeable pesticide residue on the day of application. Further, HED assumes that 10% dissipates per day post-application.

In this case for scouting and irrigation activities in corn and scouting activities in pasture/range, a TC of 1000cm^2/hr is used in the following convention to estimate exposure and risk to agricultural workers from post-application exposure.

Surrogate Dislodgeable Foliar Residue -

DFR = application rate (lb a.i./A) * 20% available as dislodgeable residue * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 or 1.08 x 10^{-3} ft^2/cm^2

and the Average Daily Dose
ADD = DFR (µg/cm^2 * TC (cm^2/hr) * hr/day * 0.001 mg/µg * 1/60 kg bw ∴

0.25 lb a.i./A * .20 * 4.54^8 µg/lb * 2.47^{-8} A/cm^2 = 0.56 µg/cm^2 ∴

0.56 µg/cm^2 * 1000 cm^2/hr * 8 hr/day * 0.001 mg/µg * 15% dermal absorption * 1/60 kg bw = 0.011 mg/kg bw/day

Since **MOE = NOAEL ÷ ADD** then 45 mg/kg bw/day ÷ 0.011 mg/kg bw/day = **4000**. Since the MOE for the anticipated post-application activities ≥ 100 it does exceed HED's level of concern.

INCIDENTS

The Incident Data System (24 July 01) indicated that there is one "probable certainty" entry associated with dicamba from a 1993 report referring to domestic animals. The Incident Data System lists 12 incidents for diflufenzopyr from a report on 11 June 1999.

RESTRICTED ENTRY INTERVAL (REI)

The copy of the label (EPA Reg. No. 7969-150, "Accepted with COMMENTS In EPA Letter Dated OCT 25, 1999") given to HED lists an REI of 12 hours (page 3). Dicamba is listed as Toxicity Category II for Primary Eye Irritation and Primary Skin Irritation (see APPENDIX I). The interim Worker Protection Standard (WPS) REI for compounds exhibiting Toxicity Category II effects for primary eye and skin irritation is 24 hours (40 CFR Part 156 § 156.208 (c) (1) and (2). **HED suggests confirmation of the basis for a 12 hour REI for this product.**

APPENDIX I

ACUTE TOXICITY OF DICAMBA

Guideline No.	Study Type	MRID NO.	Results	Toxicity Category
81-1	Acute Oral	00078444	LD_{50} = 2740 mg/kg	III
81-2	Acute Dermal	00241584	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	00263861	LC_{50} = >5.3 mg/L	IV
81-4	Primary Eye Irritation	00241584	Irritant	II
81-5	Primary Skin Irritation	00237955	Irritant	II
81-6	Dermal sensitization	00263861	Non sensitizer	N/A

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	LOAEL = 300 UF = 300	Clinical signs of neurotoxicity	Acute Oral Neurotoxicity / Rat
	Acute RfD = 1 mg/kg		
Chronic Dietary	NOAEL = 45 UF = 100	Decreased pup growth	Multi-generation Reproduction Study / Rat
		Chronic RfD = 0.45 mg/kg/day	
Incidental Oral, Short-/ Intermediate-Term	NOAEL= 45	Decreased pup growth	Multi-generation Reproduction Study / Rat

Dermal[1], Short-/ Intermediate-/ Long-Term	Oral NOAEL= 45	Decreased pup growth	Multi-generation Reproduction Study / Rat
Inhalation[2], Short-/ Intermediate-/ Long-Term	Oral NOAEL= 45	Decreased pup growth	Multi-generation Reproduction Study / Rat

1 A dermal absorption factor of 15% should be applied to extrapolate from the oral route to the dermal route.
2 A 100 % absorption rate should be applied to extrapolate from the oral route to the inhalation route.

Taken from Memo, D. Nixon, 20 Nov 2001, TXR No. 0050280

APPENDIX II

ACUTE TOXICITY OF DIFLUFENZOPYR

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	44170139	LD_{50} > 5000 mg/kg	IV
81-2	Acute Dermal	44170140	LD_{50} > 5000 mg/kg	IV
81-3	Acute Inhalation	44170141	LC_{50} > 2.93 mg/L	IV
81-4	Primary Eye Irritation	44170142	minimally irritating	III
81-5	Primary Skin Irritation	44170143	non-irritating	IV
81-6	Dermal Sensitization	44598502	negative	
81-8	Acute Neurotoxicity	44170145	NOEL > 2000 mg/kg	

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION FOR DIFLUFENZOPYR

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary Females 13+	NOEL= 100 UF = 100	Extra ribs and other skeletal variations in the rabbit developmental study.	Rabbit Developmental Study
	Acute RfD = 1.0 mg/kg		
Acute Dietary General Population including Infants and Children	None	An appropriate endpoint attributable to a single exposure for this population subgroup was not identified in the oral toxicity studies including the maternal effects in rat and rabbit developmental studies.	
Chronic Dietary	NOEL = 26	Compensated hemolytic anemia in both sexes of dogs	52-week dog feeding study
	UF = 100	**Chronic RfD** = 0.26 mg/kg/day	
Short-Term (Dermal)	NOEL= None.	No dermal or systemic toxicity was seen at 1000 mg/kg/day in the 21 day dermal toxicity study in rabbits. Therefor this risk assessment is not required.	21 day dermal toxicity study in rabbits

Intermediate-Term (Dermal)	NOEL= None	No dermal or systemic toxicity was seen at 1000 mg/kg/day in the 21 day dermal toxicity study in rabbits. Therefor this risk assessment is not required.	
Long-Term (Dermal)	NOEL= None	The use pattern does not indicate a concern for potential dermal exposure. Therefore, this risk assessment is not required.	
Short Term (Inhalation) [a]	Oral NOEL= 58	Compensated hemolytic anemia in both sexes of dogs.	Subchronic feeding-dog.
Intermediate Term (Inhalation) [a]	Oral NOEL=58	Compensated hemolytic anemia in both sexes of dogs	Subchronic feeding-dog
Long Term (Inhalation)	NOEL=None	The use pattern does not indicate a concern for potential exposure via this route. Therefore, this risk assessment is not required.	

a = An inhalation absorption factor of 100% is required for route-to-route extrapolation since an oral NOAEL was selected for this risk assessment.

Tables taken from HIARC report on DIFLUFENZOPYR date 6 October 1998.

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